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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/627,331	07/25/2003	Arthur M. Krieg	C1039.70078US00	4362

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EXAMINER	
LE, EMILY M	
ART UNIT	**PAPER NUMBER**
1648	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/08/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/627,331	KRIEG ET AL.	
	Examiner	Art Unit	
	Emily Le	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *7/25/03+11/15/06*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *50,52,53,55-57,59,60,62-64,66-70 and 72-96* is/are pending in the application.

4a) Of the above claim(s) *87-96* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *50,52,53,55-57,59,60,62-64,66-70 and 72-86* is/are rejected.

7)☒ Claim(s) *53,60,67,73,76,79 and 84* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/14/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I, a method of treating, preventing and ameliorating a hepatitis B viral infection, and the species AACGTT in the reply filed on 11/15/2006 is acknowledged. The traversal is on the ground(s) that a search and examination of the generic claim would not constitute an undue burden.

Applicant's submission has been considered, however, it is not found persuasive. In the instant case, it should be noted that there does not exist a generic claim that encompasses both a method of treating, preventing and ameliorating hepatitis B and C viral infections.

As stated in the previous office action, inventions I-II are directed to related processes of use for oligonucleotides containing the CpG motif. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed have differing function or effect. The function of the invention of Group I is directed at providing treatment to subjects infected with hepatitis B virus; whereas, the function of the invention of Group II is directed at providing treatment for subjects infected with hepatitis C virus. Additionally, it should further be noted that HBV differs from HCV phenotypically and genotypically. Hence, a different field of search would be required for each of the listed inventions. Furthermore, the inventions as

claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants. Moreover, MPEP 808.02 provides that a serious burden can be established by showing one of the following: (A) Separate classification thereof; (B) a separate status in the art when they are classifiable together; and (C) a different field of search. In the instant case, as set forth in the previous office action, the inventions have different classification, and further have a different field of search. Thus, in accordance with the cited MPEP tenets, a serious burden would be imposed upon the Office if a restriction requirement between the inventions is not required. Therefore, the requirement is still deemed proper and is therefore made FINAL.

Status of Claims

2. Claims 1-49, 51, 54, 58, 61, 65 and 71 are cancelled. Claims 77-96 are added. Claims 50, 52-53, 55-57, 59-60, 62-64, 66-70 and 72-96 are pending. Claims 87-96 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 11/15/2006. Claims 50, 52-53, 55-57, 59-60, 62-64, 66-70 and 72-86 are under examination.

Specification

3. The disclosure is objected to because of the following informalities: It is noted that page 24 of the specification is blank. Appropriate correction is required.

4. Additionally, it is noted that the instant application also contains a preliminary amendment, filed on the same date as the filing for the instant patent application, prior to September 21, 2004. In the instant case, MPEP § 608.04 (b) provides: For

applications filed prior to September 21, 2004, a preliminary amendment that was present on the filing date of an application may be considered a part of the original disclosure if it was referred to in a first filed oath or declaration in compliance with 37 CFR 1.63. If the preliminary amendment was not referred to in the oath or declaration, applicant will be required to submit a supplemental oath or declaration under 37 CFR 1.67 referring to both the application and the preliminary amendment filed with the original application. In accordance with the teachings of MPEP 608.04(b), Applicant is required to submit a supplemental oath or declaration under 37 CFR 1.67 referring to both the application and the preliminary amendment filed with the original application.

Claim Objections

5. Claims 53, 60, 67, 76, 73, 79 and 84 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claims 53, 60, 67, 76, 79 and 84 require the nucleic acid molecules of claims 52, 59, 66, 72, 78 and 83, respectively, to have the sequence 5'-AACGTT-3'. However, it is noted that this requirement fails to further limit the respective parent claims. The parent claims requires the nucleic acid sequence to comprise the sequence 5'-purine, purine, C,G, pyrimidine, pyrimidine, C, G-3'. In the instant case, the sequence 5'-AACGTT-3' does not comprise the required C,G sequence at the 3' end. Hence, the claims fail to further limit the parent claim. This objection also affects claim 76 because it recites a dependency to claim 67.

Information Disclosure Statement

6. The information disclosure statement filed 01/14/2004 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited **foreign patent document; each non-patent literature publication** or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. In the instant case, it is also noted that the filed IDS also lists U.S. Patent and PreGrant documents. These documents have been considered, however, the information referred to in the foreign patent documents and the non-patent literature publications has not been considered.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claim 60 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 60 recites a dependency to claim 58. However, claim 58 is a cancelled claim. Since claim 58 is a cancelled claim, it is unclear what is intended to be encompassed by claim 60. For the purpose of advancing examination, the Office will interpret that it is Applicant's intention to require claim 60 to recite a dependency to claim 59. This interpretation is consistent with Applicant's presentation of the other claims, e.g. claims 52-53, 66-67, 72-73, 78-79 and 83-84.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 50, 52-53, 55-57, 59-60, 62-64, 66-70 and 72-86 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claimed invention is a method of treating, preventing or ameliorating a hepatitis B viral infection in a subject with the administration of an oligonucleotide comprising at least one unmethylated CpG motif to the subject.

The basic inquiry for possession is: Can one skilled in the art reasonably conclude that the inventor was in possession of the claimed invention at the time the application was filed? If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, *even if every nuance of the claim is not explicitly described in the specification*, then the requirement for an adequate written description is met.

To provide adequate written description and evidence of possession, the specification must provide sufficient description of the claimed invention by i) actual reduction to practice, ii) reduction to drawings; or iii) disclosure of relevant identifying characteristics, such as disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, correlation between structure and function, and methods of making the claimed invention. The analysis:

i) Sufficient description of the claimed invention by actual reduction to practice: The specification does not teach of a single oligonucleotide containing the CpG motif that treats, prevents or ameliorate hepatitis B viral infection. Hence, the disclosure fails to evidence that Applicant is in possession of the claimed invention by actual reduction to practice. It should be noted here that the only reference to hepatitis B virus is disclosed at line 20, page 14 of the instant specification. At the cited passage, taken in context, Applicant discloses that hepatic B virus is an example of infectious virus that causes an "immune system deficiency" in a subject. Beside this cited passage, the instant specification does not set forth any guidance or teachings directed to hepatitis B virus, and the prevention, treatment, and amelioration hepatitis B viral infection.

ii) Sufficient description of the claimed invention by reduction to drawings: The instant patent application is filed with many drawings. However, none of the drawings provided sets forth an oligonucleotide comprising the CpG motif that treats, prevents or ameliorate hepatitis B viral infection. Hence, the disclosure fails to evidence that Applicant is in possession of the claimed invention by reduction to drawings.

iii) iii) disclosure of relevant identifying characteristics: The disclosure fails to provide relevant identifying characteristics relating to the claimed invention. The disclosure fails to set forth the complete structure of an oligonucleotide that treats, prevents or ameliorate hepatitis B viral

infection. The disclosure does not even set forth the partial structure of oligonucleotides containing the CpG motif that treat, prevent or ameliorate hepatitis B viral infection. The disclosure further failed to set forth the physical and chemical properties of oligonucleotides encompassed by the claimed invention. Furthermore, the disclosure failed to set forth any functional characteristics that oligonucleotides containing the CpG motif must possess to treat, prevent or ameliorate hepatitis B viral infection. As stated above, beside the one reference to hepatitis B virus, line 20, page 14 of the specification, Applicant has not set forth any additional teachings relating the administration of an oligonucleotide comprising the CpG motif to treat, prevent or ameliorate hepatitis B viral infection.

In the instant, nothing exists in the specification to demonstrate that Applicant is in possession of an oligonucleotide containing the CpG motif that treats, prevents and ameliorate hepatitis B viral infection in vertebrate subjects. In the absence of any evidence demonstrating that Applicant is in possession of the primary active ingredient for the claimed invention, oligonucleotides comprising the CpG motif that treat, prevents or ameliorate hepatitis B viral infection, the skilled artisan cannot reasonably conclude or recognize that Applicant is in possession of the claimed invention at the time the invention was filed. The specification is fatally defective in this regard.

Applicant is reminded that that written description requirement is separate and distinct from the enablement requirement.

11. Claims 50, 52-53, 55-57, 59-60, 62-64, 66-70 and 72-86 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. In Genentech *Inc. v. Novo Nordisk* 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997); *In re Wright* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); See also *Amgen Inc. v. Chugai Pharm. Co.,* 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir. 1991); *In re Fisher* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Further, in *In re Wands* 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) the court stated:

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman* [230 USPQ 546, 547 (Bd Pat App Int 1986)]. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Breadth of the claims:

The claimed method of treating, preventing or ameliorating hepatitis B viral infection in a subject with the administration of an oligonucleotide comprising at least one unmethylated CpG motif to the subject.

The specification provides the following,

A "subject" shall mean a human or vertebrate animal including a dog, cat, horse, cow, pig, sheep, goat, chicken, monkey, rat, and mouse. [Lines 31-32, page 19.]

Hence, the breadth of the claims is directed to a method of treating, preventing or ameliorating hepatitis B viral infection in a subject with the administration of an oligonucleotide comprising at least one unmethylated CpG motif to the subject. The subjects encompassed by the claimed invention are all vertebrate animals, including humans.

Presence or Absence of working examples:

The specification does not contain any working examples that are directed to the claimed invention, a method of treating, preventing or ameliorating hepatitis B viral infection in a subject with the administration of an oligonucleotide comprising the CpG motif. The specification does not containing any working examples demonstrating that such oligonucleotides treat, prevent or ameliorate hepatitis B viral infection. Nothing exists in the specification demonstrating that fundamental research has been conducted to support Applicant's claim, wherein oligonucleotides comprising the CpG motif treat, prevent or ameliorate hepatitis B viral infection in vertebrate subjects.

Amount of direction or guidance present in the specification:

The specification does not contain any evidence demonstrating that oligonucleotides containing the CpG motif treat, prevent or ameliorate hepatitis B viral infection in vertebrate subjects. All that is present in the specification are conjectures of

potential application of such oligonucleotides in the treatment, prevention and amelioration of viral infections in vertebrate subjects.

Nature of the invention

Based on Applicant's disclosure, it appears that the nature of the claimed invention is directed to the use of the art recognized immunostimulatory activity of oligonucleotides containing the CpG motif, including the induction of Th1 immune response invoked by the production of Th1 associated cytokines accorded by the CpG motif to render a therapeutic value, wherein the desired therapeutic value is to provide treatment, prevention and amelioration of hepatitis B viral infection in vertebrate subject--immunotherapy.

State of the Art:

In the instant, the involvement of a Th1 type immune response in combating against intracellular pathogens is a well-recognized general concept. The art acknowledges the importance of Th1 type immune response, which is stimulated by the production of Th1 associated cytokines, in the elimination of intracellular pathogens, including viruses. However, the art has not accredited or recognized any one particular Th1-associated cytokine to the treatment, prevention and amelioration of viral infection in a subject. Specifically, the art teaches that while cytokines secreted by T helper cells are of critical importance for the outcome of many infectious diseases, the production of the "right" set of cytokines can be a matter of life or death, as noted by Infante-Duarte et al. Infante-Duarte et al. further notes that in addition to a Th1 type immune response, a Th2 type immune response is also necessary. Specifically, Infante-Duarte et al.

teaches that a tight control over where and when Th1 and Th2 immune responses happen is necessary to keep intracellular infections under control, and to prevent the Th1 type immune response from causing damage to the host.[1] Hence, while the importance of a Th1 type immune response is well recognized in the art, the art further notes that a balance between Th1 and Th2 type immune responses is necessary to resolve an infection.

The cytokine art also provides that the efficacy of Th1 associated cytokines, such as interleukin 2, interleukin 12 and interleukin 18, against intracellular pathogens are controversial, as evidenced by Aoki et al.,[2] Bohn et al.,[3] Sakao et al.,[4] Zaitseva et al.,[5] and Masihi, K.[6] Aoki et al. teaches that while interleukin 2 may confer good protection for non-pathogenic mycobacterial strain Bacille Calmette-Guerin (BCG), interleukin 2 does not confer protection for virulent *M. bovis* infection. Bohn et al. teaches that interleukin-12, a Th1 associated cytokine, induces different effector mechanisms that result in either protection or exacerbation of a disease. Specifically, Bohn et al. notes that the administration of exogenous interleukin 12 confers protection against Yersinia enterocolitica in susceptible BALB/c mice, but exacerbates yersiniosis in resistant C57BL/6 mice. Sakao et al. teaches that interleukin 18, a Th1 associated cytokine, is

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[1] Infante-Duarte et al., Th1/Th2 balance in infection. Springer Seminars in Immunopathology, 1999, 21: 317-338. [Paragraph bridging pages 321-322, in particular.]
[2] Aoki et al. Use of cytokines in infection. Expert Opin. Emerg. Drugs, 2004, vol. 9, No. 2, 223-236. [Lines 4-15, left column, page 229,in particular]
[3] Bohn et al., Ambiguous role of interleukin-12 in Yersinia enterocolitica infection in susceptible and resistant mouse strains. Infect. Immune., 1998, Vol. 66, 2213-2220. [Abstract, in particular.]
[4] Sakao et al. IL-18-deficient mice are resistant to endotoxin-induced liver injury but highly susceptible to endotoxin shock. Int. Immunol., 1999, Vol. 11, 471-480. [Abstract, in particular.]
[5] Zaitseva et al. Interferon gamma and interleukin 6 modulate the susceptibility of macrophages to human immunodeficiency virus type 1 infection. Blood, 2000, Vol. 96, 3109-3117. [Abstract, in particular]

responsible for the progression of endotoxin-induced liver injury in mice primed with interleukin 18. Zaitseva et al. teaches that both interleukin 6 and interferon gamma augment the susceptibility of monocyte-derived macrophages to infection. Masihi, K. notes that interleukin 2 increases the production of HIV in vitro, and enhances the translocation of bacteria from intestines to other organs in animal studies. In summation, the art teaches that cytokines can be inherently toxic, have unclear pharmacological behavior and also have pleiotropic effects. Hence, the art recognizes that the use of cytokine to direct treatment is unpredictable and complicated.

Additionally, while the art teaches that oligonucleotides containing the CpG motif are capable of stimulating a Th1 type immune response, however, the art also teaches that the Th1 associated cytokine profile for these oligonucleotides vary from one oligonucleotide and species of subject to the next, as evidenced by Krieg et al.[7] and Mutwiri et al.[8] Krieg et al notes that each oligonucleotide containing the CpG motif must be considered as a separate agent because the quality and type of immune stimulation induced by these oligonucleotides varies. Krieg et al. particularly notes that the type of cytokine stimulated by oligonucleotides containing the CpG motif is distinct from one oligonucleotide to the next. Additionally, both Krieg et al. and Mutwiri et al. note that the level and type of immune stimulation varies depending on i) the specific nucleic acids, purines and pyrimidines, surrounding the CpG motif; ii) the spacings

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[6] Masihi, K. Fighting infection using immunomodulatory agents. Expert Opin. Biol. Ther., 2001, Vol. 1, No. 4, 641-653. [Lines 15-25, left column of page 646, in particular]
[7] Krieg et al., CpG motif in bacterial DNA and their immune effects. Annu. Rev. Immunol., 2002, Vol. 20, 709-760. [paragraph that bridge pages 716-717, in particular.]

between CpG motifs; iii) the numbers of CpG motifs in an oligonucleotide; iv) the absence or presence of a CpG motif to the end of the oligonucleotide; and v) the context in which the CpG motif is presented in the sequence.

The CpG art further teaches that the immunostimulatory activity of oligonucleotides containing the CpG is very species specific, as evidenced by Mutwiri et al. Table 1 of Mutwiri et al. provides that the *in vitro* immunostimulatory activity of oligonucleotides containing the CpG motif varies from one species to the next. Mutwiri et al. also notes that the level of immunostimulating induced by a particular oligonucleotide is also dependent on the sequence(s) flanking the CpG motif. Specifically, Mutwiri et al. notes that the GTCGTT motif, which is the optimal motif for humans, is optimal for stimulation of lymphocyte proliferation in several species including cattle, sheep, goats, horses, pigs, dogs, cats and chickens; whereas the murine CpG motif (GACGTT) is only optimal for inbred rabbits and mice.

Furthermore, both Krieg et al. and Mutwiri et al. sets forth that the recognition of the CpG motifs requires Toll-like receptor (TLR) 9, wherein cells that express TLR-9 produce Th1 associated cytokines. However, Mutwiri et al. provides that TLR-9 has only been identified in mice and humans. Mutwiri et al. also provides that the TLR-9 is differentially expressed in humans and mice. Hence, if the recognition of the CpG motif were dependent of TLR-9, then it would logically follows that the extent of the Th1 type immune response induced by the oligonucleotide would necessarily vary from one

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[8] Mutwiri et al. Biological activity of immunostimulatory CpG DNA motifs in domestic animals. Veterinary Immunology and Immunopathology, 2003, Vol. 91, 89-103. [See 2nd and 3rd full paragraphs, left column of page 93; last sentence of paragraph bridging pages 89-90.]

species to the next. Mutwiri et al. also sets forth that *in vitro* observations do not accurately predict what happens *in vivo*.

Moreover, the potential use of oligonucleotides containing the CpG motif to stimulate a Th1 type immune response that treats and prevents infection is widely speculated in the art. However, efforts to harness the immunostimulatory activity of oligonucleotides containing the CpG motif to trigger an innate immune response that protect a host from infectious pathogen has proven to be challenging and elusive, as evidenced by Yamamoto et al.,[9] Equils et al.,[10] Agrawal et al.,[11] and Olbrich et al.[12] Yamamoto et al. reports that oligonucleotides containing the CpG motif failed to improve the survival in mice challenged with influenza. Equils et al. teaches that such oligonucleotides can induce the HIV transcriptional regulatory elements in long terminal repeats, increasing viral replication. Agrawal et al. teaches that HIV-infected humans treated with oligonucleotides containing the CpG motif showed dose-dependent increases viral load. Lastly, Olbrich et al. teaches that the administration of oligonucleotides containing the CpG motif accelerated and increased the severity of Friend retrovirus in mice. In the case of Olbrich et al., the author notes that the use of oligonucleotides containing the CpG motif for the treatment of viral infection may be a double edge sword that can resolute in effective therapy but also in acceleration of

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[9] Yamamoto et al., Oligodeoxyribonucleotides with 5'ACGT-3' or 5TCGA-3 sequence induce production of interferons. Curr. Top. Microbiol. Immunol. 2000, Vol. 247, 23-40.
[10] Equils et al. Toll-like receptor 2 (TLR2) and TLR9 signaling resulted from HIV-long terminal repeat transactivation and HIV replication in HIV-1 transgenic mouse spleen cells: implications of simultaneous activation of TLRs on HIV replication. J. Immunol. 2003, 170, 5159-5164.
[11] Agrawal, et al. Was induction of HIV1 through TLR9? J. Immunol. 2003, 171, 1621-1621.
[12] Olbrich et al. Preinfection treatment of resistant mice with CpG oligodeoxynucleotides renders them susceptible to friend retrovirus-induced leukemia. J. Virol., 2003, 77, 10658-10662.

disease. Olbrich et al. notes that this double edge sword observation may be dependent on the time point of treatment.

Hence, overall, the literature notes the use of CpG to stimulate the production of cytokines, the use of cytokines to influence viral infection, and the development of a treatment regimen for diseases is unpredictable and complicated.

Predictability or unpredictability of the art:

As discussed above, the art recognizes that the use of cytokine to direct treatment is unpredictable and complicated. The art also recognizes that use of CpG to stimulate cytokine production, the use of the induced cytokine to influence viral infection, and the development of treatment regimen unpredictable and complicated. The art additionally teaches that the efforts to harness the immunostimulatory activity of oligonucleotides containing the CpG motif to trigger an innate immune response that protects a host from infectious pathogen has proven to be challenging and elusive.

Quantity of experimentation necessary:

Extreme undue burden of experimentation would be imposed upon the skilled artisan practicing the claimed invention. As stated above, Applicant has not provided much, if any, guidance or direction relating to the claimed invention. All that Applicant has provided is a conclusion that is made on the basis of generalized concepts that are well known in the art. And the formation of a conclusion based on generalized concepts renders the conclusion flawed. Generalized concepts are directed to support a general direction of studies or research; however, they do not support concrete conclusions. Concrete conclusions must be substantiated by facts, including evidence. In the instant,

while the general direction of research may be outlined for the skilled artisan, the skilled artisan would not readily be able to practice the claimed invention without the undue burden of experimentation. The path that the skilled artisan must take in his research is marked with many challenges that are recognized in the art, including the complex nature of oligonucleotides containing CpG motif and the complexity of the immune system, including the Th1 type immune response and the functional characteristics of its associated cytokines. Hence, in view of the lack of any guidance in the specification concerning the effective use of oligonucleotides to treat, prevent or ameliorate viral infection in a subject; the unpredictability of oligonucleotides containing CpG motif to stimulate specific immune response; and the inherent toxicity, the unclear pharmacological behavior, and the pleiotropic effects of cytokines; the skilled artisan would not be able to reasonably practice the claimed invention without an undue burden experimentation. Thus, the claims are rejected under 35 U.S.C § 112, 1st paragraph for failing to comply with the enablement requirement.

A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F. 2d 1557, 1562, 27 USPQ 2d 1510, 1513 (Fed. Cir. 1993).

Double Patenting

12. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the

unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In *re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

13. Claims 50, 55-57, 62-64, 68-70 and 74-77, 80-82 and 85-86 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 59-61, of copending Application No. 11/255100.

The claimed invention is directed to a method of treating, preventing and ameliorating hepatitis B viral infection with the administration of an oligonucleotide comprising the CpG motif.

Claims 59-61 of the conflicting patent application is directed to a method of treating hepatitis B viral infection with the administration of an oligonucleotide comprising the CpG motif, SEQ ID NO: 27, to a subject having or at risk of HBV infection.

The difference between the claims is: claims 59-61 of the conflicting patent application is directed to the administration of a specific oligonucleotide. However, the claimed invention recites the transitional term "comprising". Hence, the claimed invention also encompasses the species of oligonucleotides recited in the claims of the conflicting patent application. In the instant, the species of oligonucleotides recited in claims 59-61 of the conflicting patent application is encompassed by the genus of oligonucleotides recited in the claims of the instant patent application. Thus, the species of oligonucleotides recited in claims 59-61 of the conflicting patent application anticipates the genus of oligonucleotides recited in the claims of the instant patent application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

14. Claims 50, 55-57, 62-64, 68-70 and 74-77, 80-82 and 85-86 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 40 and 97 of copending Application No. 10/613524. Although

the conflicting claims are not identical, they are not patentably distinct from each other because:

Claim 97 of the conflicting patent application is directed at a method for preventing disease in a subject with the administration of an oligonucleotide comprising the CpG motif, wherein the oligonucleotide has the sequence of SEQ ID NO:1.

The difference between the claim sets is: Claim 97 of the conflicting patent application is limited to the administration of a specific oligonucleotide. However, the claimed invention recites the transitional term "comprising". Hence, the claimed invention also encompasses the species of oligonucleotides recited in the claims of the conflicting patent application. In the instant, the species of oligonucleotides recited the conflicting patent application is encompassed by the genus of oligonucleotides recited in the claims of the instant patent application. Thus, the species of oligonucleotides recited the conflicting patent application anticipates the genus of oligonucleotides recited in the claims of the instant patent application.

The other difference noted between the claim sets is: Claim 97 of the conflicting patent application is non-specific as to the type of diseases intended. However, it is noted that claim 40 of the conflicting patent application suggests the administration of SEQ ID NO: 1 to treat and prevent an infectious disease. To further understand the type of disease(s) intended by the claim, the Office looked to the specification. It is noted that the specification lists hepatitis B virus infection as a disease intended by Applicant. [Paragraph [0022] of the application's PreGrant publication] Hence, in the

instant, the conflicting patent application is also directed at a method of treating and preventing hepatitis B viral infection.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

15. Claims 50, 52-53, 55-57, 59-60, 62-64, 66-70 and 72-86 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 19-33, of copending Application No. 10/987146.

Claims 19-33 of the conflicting patent application is directed at a method for treating viral infection with the administration of an oligonucleotide comprising the CpG motif to said subject.

The difference between the claim sets is: the conflicting patent application is not limiting to the type of viral infection it intends to treat. However, in view of the disclosure of the conflicting patent application, by viral infection, Applicant intends to encompass hepatitis B viral infections. See line 19, page 13 of the conflicting patent application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

16. Claims 50, 55-57, 62-64, 68-70, 74-77, 80-82 and 85-86 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 47, 52, 57, 72 and 74, of copending Application No. 11/071836.

Claims 47, 52, 57, 72 and 74 of the conflicting patent application is directed at a method for treating viral infection with the administration of an oligonucleotide

comprising the CpG motif to said subject, wherein the oligonucleotide has the sequence of SEQ ID NO: 46.

The difference between the claim sets is: the conflicting patent application requires the oligonucleotide to comprise SEQ ID NO: 46, whereas, the claimed invention is not limiting to a particular sequence. However, the claimed invention recites the transitional term "comprising". Hence, the claimed invention also encompasses the species of oligonucleotides recited in the claims of the conflicting patent application. In the instant, the species of oligonucleotides recited in the conflicting patent application is encompassed by the genus of oligonucleotides recited in the claims of the instant patent application. Thus, the species of oligonucleotides recited the conflicting patent application anticipates the genus of oligonucleotides recited in the claims of the instant patent application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Note: Some of the rejections stated above, in part, based on the specification of a previously issued patent, rather than the claims. In support of the use of this material, the examiner notes the following excerpt from MPEP section 804 II(B)(1):

> When considering whether the invention defined in a claim of an application is an obvious variation of the invention defined in the claim of a patent, the disclosure of the patent may not be used as prior art. This does not mean that one is precluded from all use of the patent disclosure.

The specification can always be used as a dictionary to learn the meaning of a term in the patent claim. In re Boylan, 392 F.2d 1017, 157 USPQ 370 (CCPA 1968). Further, those portions of the specification which provide support for the patent claims

may also be examined and considered when addressing the issue of whether a claim in the application defines an obvious variation of an invention claimed in the patent. In re Vogel, 422 F.2d 438, 441-42, 164 USPQ 619, 622 (CCPA 1970). The court in Vogel recognized "that it is most difficult, if not meaningless, to try to say what is or is not an obvious variation of a claim," but that one can judge whether or not the invention claimed in an application is an obvious variation of an embodiment disclosed in the patent which provides support for the patent claim. According to the court, one must first "determine how much of the patent disclosure pertains to the invention claimed in the patent" because only "[t]his portion of the specification supports the patent claims and may be considered." The court pointed out that "this use of the disclosure is not in contravention of the cases forbidding its use as prior art, nor is it applying the patent as a reference under 35 U.S.C. 103, since only the disclosure of the invention claimed in the patent may be examined."

Thus, the courts have held that it is permissible to use the specification in determining what is included in, and obvious from, the invention defined by the claim on which the rejection is based. This is true even where elements are drawn from the specification describing the claimed invention which are not elements in the claim itself.

Conclusion

17. No claims are allowed.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Emily Le whose telephone number is (571) 272 0903. The examiner can normally be reached on Monday - Friday, 8 am - 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce R. Campell can be reached on (571) 272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Emily M. Le 1/31/07
Patent Examiner
Art Unit 1648

E.Le